

The Renin Angiotensin System in the Human Esophageal Mucosa

– expression, actions and potential involvement in reflux disease

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- I.** Björkman E, Casselbrant A, Lundberg S, Fändriks L.
In vitro assessment of epithelial electrical resistance in human esophageal and jejunal mucosae and in Caco-2 cell layers. *Scand J Gastroenterol.* 2012 Nov;47(11):1321-33.
- II.** Björkman E, Edebo A, Casselbrant A, Helander HF, Bratlie SO, Vieth M, Fändriks L.
The renin angiotensin system in the esophageal mucosa of healthy subjects and patients with reflux disease. *Accepted Scand J Gastroenterol.* 2012.
- III.** Björkman E, Edebo A, Fändriks L, Casselbrant A. In vitro actions by angiotensin IV on the esophageal epithelium in healthy subjects and GERD patients. *In manuscript*



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ABSTRACT

The renin angiotensin system (RAS) is a classical endocrine system, regulating body fluid balance and blood circulation. Recent research has shown that the system is being also locally expressed and active in several organs and tissues. Components of RAS have been discovered throughout the gastrointestinal tract and have, in addition, been found in the human esophagus. It was hypothesised that RAS could be of interest in relation to gastroesophageal reflux disease (GERD), which is a prevalent clinical condition, where gastric content backflows into the esophagus and causes troublesome symptoms. The general aim of the present thesis was to confirm the presence and further investigate RAS in healthy and reflux exposed human esophageal mucosae.

Esophageal biopsies were collected from healthy volunteers and GERD patients. The gene activity and protein expression of various RAS components were investigated using RT-PCR, western blot, ELISA and immunohistochemistry. The square wave current pulse analysis was investigated for its applicability in Ussing chambers for assessing mucosal *epithelial* resistance (R_{ep}), which in turn permits calculation of the epithelial ion current (I_{ep}).

All investigated RAS components were detected and several of these were significantly altered in relation to reflux disease. Particular attention was paid to the induced expression of the angiotensin II type 2 receptor (AT2R), and to the reduced expression of the angiotensin IV (AngIV) receptor (AT4R) in certain areas in the mucosae from patients with erosive reflux disease (ERD). Using the validated Ussing chamber method, it was found that biopsies from reflux exposed mucosa exhibited lower R_{ep} and higher I_{ep} at baseline. Upon AT2R stimulation the healthy individuals responded with increased I_{ep} , while no significant change was observed in relation to ERD, despite the higher AT2R expression. The peptide AngIV also stimulated the net epithelial current, although the response was small in the mucosae from ERD patients.

The thesis demonstrates that a substantial local RAS is present in the human esophageal mucosa, and it is likely that also angiotensins other than Angiotensin II are produced. Particularly, the AT2R seems to have reduced response capability in individuals with reflux disease. The expressional and functional alterations suggest that RAS might be involved in the pathophysiology of GERD.

Key words: endoscopic biopsies, epithelial electrical current, epithelial electrical resistance, esophageal mucosae, gastroesophageal reflux disease, mucosal barrier integrity, renin angiotensin system